REMARKS

Upon entry of the current amendments, claims 54-74 are currently pending. Claims 1-53 were cancelled in a Preliminary Amendment filed November 10, 2003. Claims 54, 57, and 60 have been amended. Claims 63-74 have been added.

Amendments

Claims 54, 57, and 60 have been amended to correct grammatical errors and to clarify the invention. Support for new claims 63-74 can be found, *inter alia*, throughout the specification, as filed, including pages 52 and 60-62.

No new matter has been introduced by way of these amendments.

The amendments herein are made solely to promote the prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional applications(s).

Supplemental IDS

Applicants herein submit a supplemental Information Disclosure Statement (IDS). It is respectfully requested that the information cited therein be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

Substitute Drawings

Applicant respectfully requests confirmation of entry of one set (twenty-three sheets, twenty-three figures) of substitute formal drawings previously submitted to the U.S. Patent and Trademark office on March 12, 2004.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 54-62 are rejected under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse this rejection for the reasons stated below.

Typographical Error in Claim 54

The Examiner states that the specification, while being enabling for a method of treating a subject by administration of an anticancer agent, CPT-11 and JBT 3002 in multilamellar vesicles to reduce intestinal damage (intestinal mucositis), allegedly does not reasonably provide enablement for a method of treating a subject with any *neoplastic* agent and JBT 3002 to alleviate or prevent any side effects including myelosuppression, oral mucositis, esophageal mucositis, and peripheral neuropathy.

Applicants would like to note that the use of the term, "neoplastic agent," in claim 54 was a typographical error. Claim 54 has been amended to read, "anti-neoplastic agent." Applicants respectfully submit that this amendment sufficiently addresses the Examiner's assertion that the specification "does not reasonably provide enablement for a method of treating a subject with any **neoplastic** agent and JBT 3002 to alleviate or prevent any side effects ...."

Focus on Mucositis

The Examiner alleges that the specification does not include working examples that combine JBT 3002 with any anti-neoplastic agent or neoplastic agent to alleviate myelosuppression and peripheral neuropathy. Applicants respectfully submit that the specification enables the artisan

of ordinary skill to use JBT 3002 with any anti-neoplastic agent to alleviate myelosuppression and peripheral neuropathy. However, in order to expedite the prosecution of this application, Applicants have amended the pending claims in order to focus on the prevention, alleviation, or amelioration of mucositis.

Prevention of Mucositis

The Examiner alleges that the specification is not enabling for "prevention" of side effects. Applicants respectfully traverse this assertion. Applicants respectfully direct the Examiner's attention to, *inter alia*, Example 14 on pages 60-22 of the specification. The protocol disclosed in Example 14 clearly states that treatment with JBT 3002 was *followed by* treatment with CPT-11. In the discussion summarizing the results, it is clearly stated that treatment with JBT 3002 followed by CPT-11 *prevents* disruption of the intestinal architecture as demonstrated through hematoxylin and eosin (H&E) staining of pathology samples. This example clearly demonstrates how the prior administration of JBT 3002 can prevent mucositis associated with anti-neoplastic therapy.

Undue Experimentation

The Examiner alleges that the disclosure does not demonstrate sufficient evidence to support the Applicants' claim to alleviating myelosuppression, peripheral neuropathy, and mucositis in any subject by administration of JBT3002 and any anti-neoplastic agent.

Applicants respectfully submit that the specification enables the artisan of ordinary skill to use JBT 3002 and any anti-neoplastic agent in a subject to alleviating myelosuppression, peripheral neuropathy, and mucositis. However, in order to expedite the prosecution of this application, independent claims 54, 57, and 60 have been amended to focus on the prevention, alleviation, or amelioration of mucositis. Furthermore, new claims 63, 66, and 69 include the phrase "wherein said JPT3002 alleviates or prevents said mucositis by upregulating expression of endogenous IL-15".

Therefore, the pending claims do not claim an anti-neoplastic agent and JBT 3002 to alleviate *any* side effects, but rather claim an anti-neoplastic agent and JBT 3002 to alleviate or prevent mucositis. In addition, the pending claims do not claim *any* anti-neoplastic agent, but rather those anti-neoplastic agents that result in modified IL-15 levels in a subject.

Smorenburg *et al.*, cited by the Examiner, describes the use of two or more drugs used in *combination* for their *anti-neoplastic* effects (combination therapy). This is in contrast with the claimed invention, which discloses a method of using JBT 3002, *not as an anti-neoplastic agent*, but as an agent that prevents or alleviates a specific side effect (mucositis) in a subject, before, during, or after being treated with an anti-neoplastic agent.

However, even if the claimed invention were to be characterized as combination therapy, Smorenburg *et al.* directly counters the Examiner's assertion that combination drug therapy is not routine in the prior art. In the very first sentence of the Introduction, Smorenburg *et al.* unequivocally state that "[c]urative cancer chemotherapy *nearly always* consists of a *combination* of cytotoxic agents", stressing how combination drug therapy is *routine*. (Emphasis added.)

Also, Smorenburg *et al.* clearly demonstrate the high level of knowledge and the great skill of those in the art. Smorenburg *et al.* illustrate how the skilled artisan learns to use two drugs together safely and effectively. For example, at page 2312, Smorenburg *et al.* teach the use of preclinical studies to discover which dosing schedules result in synergism between two drugs. Specifically, Smorenburg describes results of a preclinical study showing that sequential exposure to methotrexate for 12 hours followed by paclitaxel for 12 days "clearly showed synergism". Furthermore, Smorenburg *et al.* illustrate the use of clinical studies to discover what toxicity may result when two drugs are used together. Specifically, at page 2312, Smorenburg describes results of a clinical study showing that using paclitaxel and methotrexate together could result in occasional neutropenia and neurotoxicity.

In conclusion, Smorenburg *et al.* show that the experimentation required for practicing combination drug therapy is not simple, but such experimentation is *routine* and well known in the

art. Indeed, Smorenburg *et al.* practically provide a roadmap for learning to practice combination drug therapy. Therefore, such experimentation *cannot* be deemed *undue* experimentation.

The Examiner states that the data presented in the figures do not conclusively show that intestinal side effects have been prevented. The Examiner also alleges that there was no demonstration of reduction of either oral or esophageal mucositis. Applicants respectfully traverse these assertions for the following reasons.

With respect to the prevention of intestinal side effects, Applicants respectfully direct the Examiner's attention to, Figure 21 and page 52 of the specification. Figure 21(A) demonstrates severe disruption of intestinal architecture in mice receiving only oral saline prior to administration of CPT-11. In stark contrast, Figures 21(B), (C), and (D) reveal remarkable preservation of intestinal architecture in mice pretreated with JBT 3002. Applicants respectfully submit that these figures clearly demonstrate the prevention of intestinal side effects with the administration of JBT 3002.

With respect to oral and esophageal mucositis, Applicants respectfully submit that demonstrating reduction of intestinal mucositis is sufficient. It is well known in the art that the oral mucosa, esophageal mucosa, and gastrointestinal mucosa share a common embryologic origin. KEITH L. MOORE, THE DEVELOPING HUMAN 227 (W.B. Saunders Co. 1982) (identifying the primitive gut as giving rise "to most of the epithelium and glands of the digestive tract"). Indeed, the "common embryologic development of the entire GI tract makes it likely that the basic pathogenesis of mucositis is similar." Sonis *et al.*, Perspective on Cancer Therapy-Induced Mucosal Injury, *Cancer* 100 (9 suppl): 1995-2025, 2001 (2004). This is not surprising, for it has long been known in the art that chemotherapeutic drugs that cause oral ulceration typically also cause gastrointestinal ulceration. *See, e.g.,* EDWIN C. CADMAN & HENRY J. DURIVAGE, *Cancer Chemotherapy, in* HARRISON'S PRINCIPLES OF INTERNAL MEDICINE TWELFTH EDITION 1587, 1592 (Jean D. Wilson et al. eds., McGraw-Hill, Inc. 1991) (listing methotrexate, floxuridine, and 5-FU as anti-cancer drugs causing both oral and gastrointestinal ulceration). Furthermore, "[w]hatever the initiating event, it is likely that mucosal barrier injury in the GI tract and the oral mucosa share

similar mechanisms." See Sonis *et al.* at 2004. It is not a new concept that intestinal, oral, and esophageal mucositis share a similar basic mechanism. It has long been known in the art that chemotherapy damages the immature mucosal cells of the oral and esophageal mucosa as it does the immature crypt cells of the intestine. Skubitz and Anderson, Oral Glutamine to Prevent Chemotherapy Induced Stomatitis: A Pilot Study, *Lab. And Clinical Med.* 127: 223-228, 223 (1996). Indeed, in the study reported by Skubitz and Anderson, the reported therapy for stomatitis (oral mucositis) was based on knowledge of *intestinal* physiology: that glutamine is the major energy source for *intestinal* epithelium. *See id.* Because glutamine supplementation was known to be effective in treating *intestinal* mucositis, glutamine supplementation was tried as a therapy for *oral* mucositis. *See id.* at 224. The fact that glutamine supplementation was effective for *oral* mucositis in addition to *intestinal* mucositis, strongly suggested that the two conditions shared a common mechanism. *See id.* at 225. Therefore, it has long been known in the art that oral, esophageal, and intestinal mucositis probably share a common mechanism and that a therapy for mucositis is likely to be effective throughout the gastrointestinal tract. *Cf. id.* Copies of the four articles discussed above are provided with the supplemental IDS filed herewith.

For the reasons presented above, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 204372000902. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By 

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